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THE UNIVERSITY OF ALBERTA

STUDIES ON THE SYNTHESIS OF PREZIZAENE AND PREZIZANOL

BY

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF

MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1983

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.....
Supervisor

.....

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Date .....July 14, 1983..

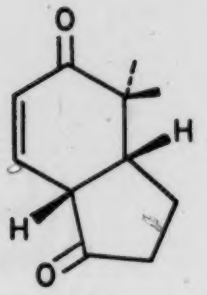
To Mother and Daddy and my husband John

for their love and inspiration

ABSTRACT

In an approach to the synthesis of the bicyclic diketone i, a potential precursor of prezizaene ii and prezizanol iii, three cyclohexenone derivatives iv, v and vi, were prepared from either commercially available 10-camphorsulfonic acid vii or α-pinene oxide viii. Treatment of 10-camphorsulfonic acid vii with fused potassium hydroxide afforded acid ix, which was reduced with lithium aluminum hydride to give the alcohol x. Oxidation of x with pyridinium chlorochromate resulted in the formation of aldehyde xi, which was also prepared directly from α-pinene oxide viii by treatment with zinc chloride. Wittig reaction of aldehyde xi with methoxymethylenetriphenylphosphorane gave vinyl ether xii. Selective hydrogenation of xii afforded the ether xiii, which was subjected to ozonolysis followed by reductive workup with zinc-acetic acid and aldol condensation with p-toluenesulfonic acid to form keto ether xiv. Treatment of keto ether xiv with boron tribromide gave bromide xv, which was hydrolyzed to the alcohol xvi by means of silver carbonate. Oxidation of alcohol xvi with pyridinium chlorochromate afforded the corresponding aldehyde iv, while oxidation with Jones reagent gave

directly the acid v. The carboxylic acid v was esterified with potassium carbonate and methyl iodide to give ester vi. Attempts to convert iv, v and vi to the bicyclic diketone i, the target molecule of these studies, are also discussed.



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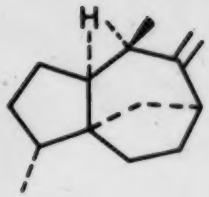

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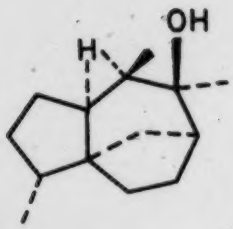

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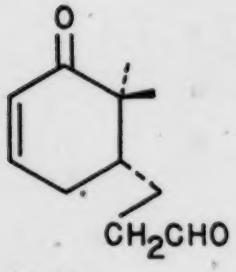

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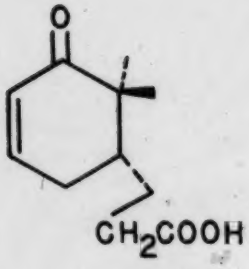

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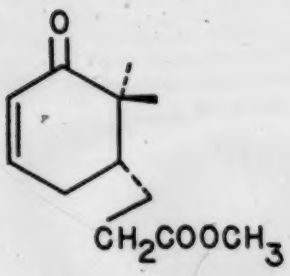

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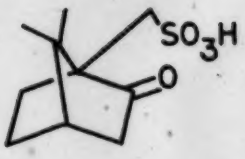

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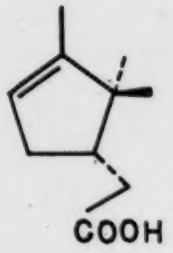

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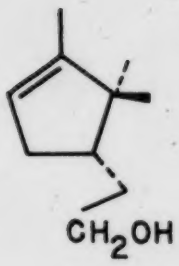

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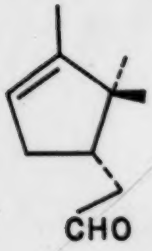

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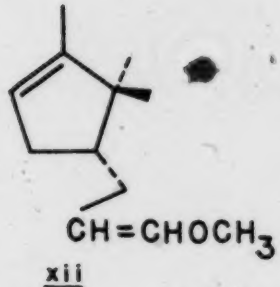

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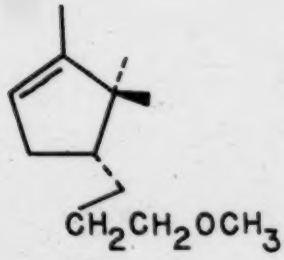

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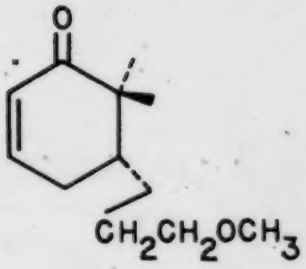

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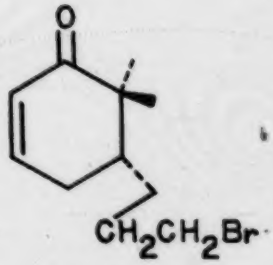

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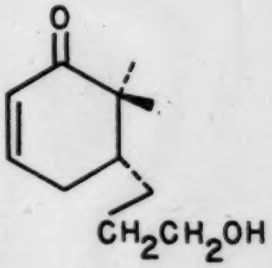

xvi

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TABLE OF CONTENTS

	Page
Abstract	v
Acknowledgments	ix
List of Figures	xi
List of Schemes	xii

STUDIES ON THE SYNTHESIS OF PREZIZAENE AND PREZIZANOL

Chapter		Page
I	Introduction	1
II	Results and Discussion	18
III	Experimental	46

* * * * * * * * * * * *

References 67

LIST OF FIGURES

	Page
Formulas 1 to 4	7
Formulas 5 to 8	8
Formulas 9 to 10	9
Formulas 11 to 13	10
Formulas 14 to 16	11
Formula 17	12
Formulas 18 to 21	13
Formulas 22 to 24	14
Formulas 25 to 26	15
Formulas 27 to 29	16
Formulas 30 to 33	17
Formulas 34 to 36	39
Formulas 37 to 42	40
Formulas 43 to 48	41
Formulas 49 to 54	42
Formulas 55 to 59	43
Formulas 60 to 64	44
Formulas 65 to 68	45

LIST OF SCHEMES

	Page
Scheme I	8
Scheme II	10
Scheme III	11
Scheme IV	12
Scheme V	14-15
Scheme VI	39
Scheme VII	45

CHAPTER I

INTRODUCTION

Zizaene (3) is the parent hydrocarbon of a small group of tricyclic sesquiterpenes found in vetiver oil. Vetiver oil is an essential oil found in the roots and rhizomes of the herbaceous plant Vetiveria zizaniodes which grows wild or is cultivated in Southern India, Indonesia, Ceylon, the Philippines, East Africa and Central America. Due to its characteristic sweet, earthy odor, it is extensively used as a raw material in the perfume industry.

The study of the biosynthesis of zizaene (3) and similar compounds with the tricyclovetivane (zizaane) skeleton 4 led to two distinct biogenetic hypotheses. The first (1) (Scheme I) proposed hinesol (6) as an intermediate. Hinesol is a spirovetivene sesquiterpene formed by a series of ring closures from farnesyl pyrophosphate (5). Cyclization of hinesol (6), followed by the chemically precedented rearrangement (7 → 8), affords zizaene (3). The feasibility of carbocation 7 rearranging to form isomer 8 was supported by the observation of Ramage and coworkers (2) that the solvolysis of alcohol 9 in refluxing pyridine/triethylamine gave ketone 10. This biosynthetic proposal was later dismissed since vetiver oil produces sesquiter-

penes enantiomeric to hinesol (6). Parallel to the biosynthesis of cedrene (Scheme II), but requiring intermediates of different relative and absolute stereochemistry, is a second biogenetic hypothesis (3-7) (Scheme III). Cedrene (13) is derived from the cation 11 possessing the alaskane skeleton, in which the isopropenyl group is cis relative to the double bond. This allows a facile Markovnikov addition to form 12. Zizaene (3) is derived from a disasteriomer of 11 having the acorane skeleton 14, in which steric constraint favors anti-Markovnikov addition to form carbocation 15.

In examining the second biogenetic scheme, Andersen noted the previously unknown skeleton of the carbocation 16. This prompted a search for a product derived from 16. Since a direct deprotonation of 16 seemed reasonable, the hydrocarbon portion of a vetiver oil sample from the island of Reunion was reexamined for exomethylene compounds related to this skeleton. In 1970, the desired molecule was isolated in reasonable amounts as its dextrorotatory isomer and designated prezizaene (1) (8). The structural assignment was made on the basis of spectral data and optical properties. The discovery of prezizaene (1) supported the theory of the biosynthesis of zizaene (3) from the

cation 16 as shown in Scheme III. Further evidence was supplied by Tomita and coworkers who succeeded in the conversion of β-acoradiene (17) to (-)-prezizaene (2) (9) by a series of chemical transformations mimicking the biogenetic process (Scheme IV).

Chemical simulation studies (7,8,10) involving acid catalyzed rearrangement of prezizaene (1) and zizaene (3) have confirmed the tendency for prezizaene (1) to undergo a [1,2] methyl shift to yield the carbon skeleton of zizaene (e.g. 8). Thus, when prezizaene (1) and zizaene (3) were individually treated with sixty percent formic acid in tetrahydrofuran, each gave the same mixture of products possessing the zizaene skeleton. The same time course for the development of each product further indicates a common intermediate species.

In 1976, Ghisalberti and coworkers (11) reported the first isolation of zizaane sesquiterpenes from a source other than vetiver oil. The steam volatile fraction of the shrub Eremophila georgei was found to consist mainly of (-)-prezizaene (2), 7β-hydroxy-(-)-prezizaene (prezizanol) (18), (-)-7β-hydroxy-2,6,6,8-tetramethyltricyclo[6.2.1.0]undecane (19), and (-)-7-oxo-2,6,6,8-tetramethyltricyclo[6.2.1.0]undecane (20). The absolute stereochemistry of these molecules

was found to be antipodal to that of the vetiver derived zizaane sesquiterpenes. Since then, prezizaene (1) has been isolated from Cupressus sempervirens and Cupressus dupreziana (12).

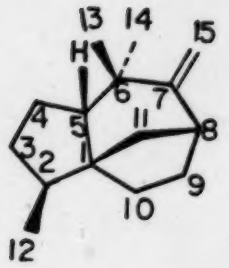
In 1978, Ganguly and coworkers (13) isolated 7β-hydroxy-(+)-prezizaene (21) from vetiver oil of the Moosanagar area of India. This new alcohol was designated (+)-allokhusiol. The same compound was isolated in 1981 from Indonesian agarwood, Aquillaria sp., by Nakanishi (14) and named jinkohol.

A total synthesis of prezizaene (2) and prezizanol (18) was published by Vettel and Coates in 1980 (15). The eighteen-step synthesis (Scheme V) produces the levorotatory isomer of prezizaene (2) from (+)-pulegone (22). The key step is an intramolecular ring expansion of the diazoethyl compound 24 to the isomeric methano-perhydroazulenones 25 and 26, formed in a ratio of 1:1.12. Of the two, only isomer 26 possesses the desired tricyclo[6.2.1.0]undecane skeleton which is useful for the subsequent conversion to prezizaene (2). The reported overall yield of the synthesis from the α-keto ester 23 was three percent.

In this laboratory, an interest in the zizaane family of compounds first resulted in the total synthesis of (-)-khusimone (27), (+)-zizanoic acid

(28), and (-)-epizizanoic acid (29) by Chan (16) in 1979. In continuation of our studies in this area, a synthesis of the bicyclic diketone 31 from α-pinene oxide (30) has been undertaken. Diketone 31 is considered to be a key intermediate towards the total synthesis of prezizaene (2) and prezizanol (18). The stereochemically controlled conversion of diketone 31 to a compound such as 32, followed by cyclization (32 → 33), would provide a facile route to the required tricyclic system of the prezizaane family.

This thesis deals with the work directed toward the synthesis of the bicyclic diketone 31.



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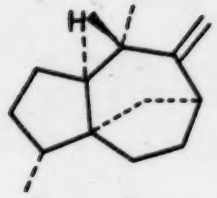

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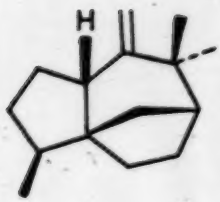

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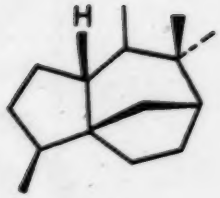

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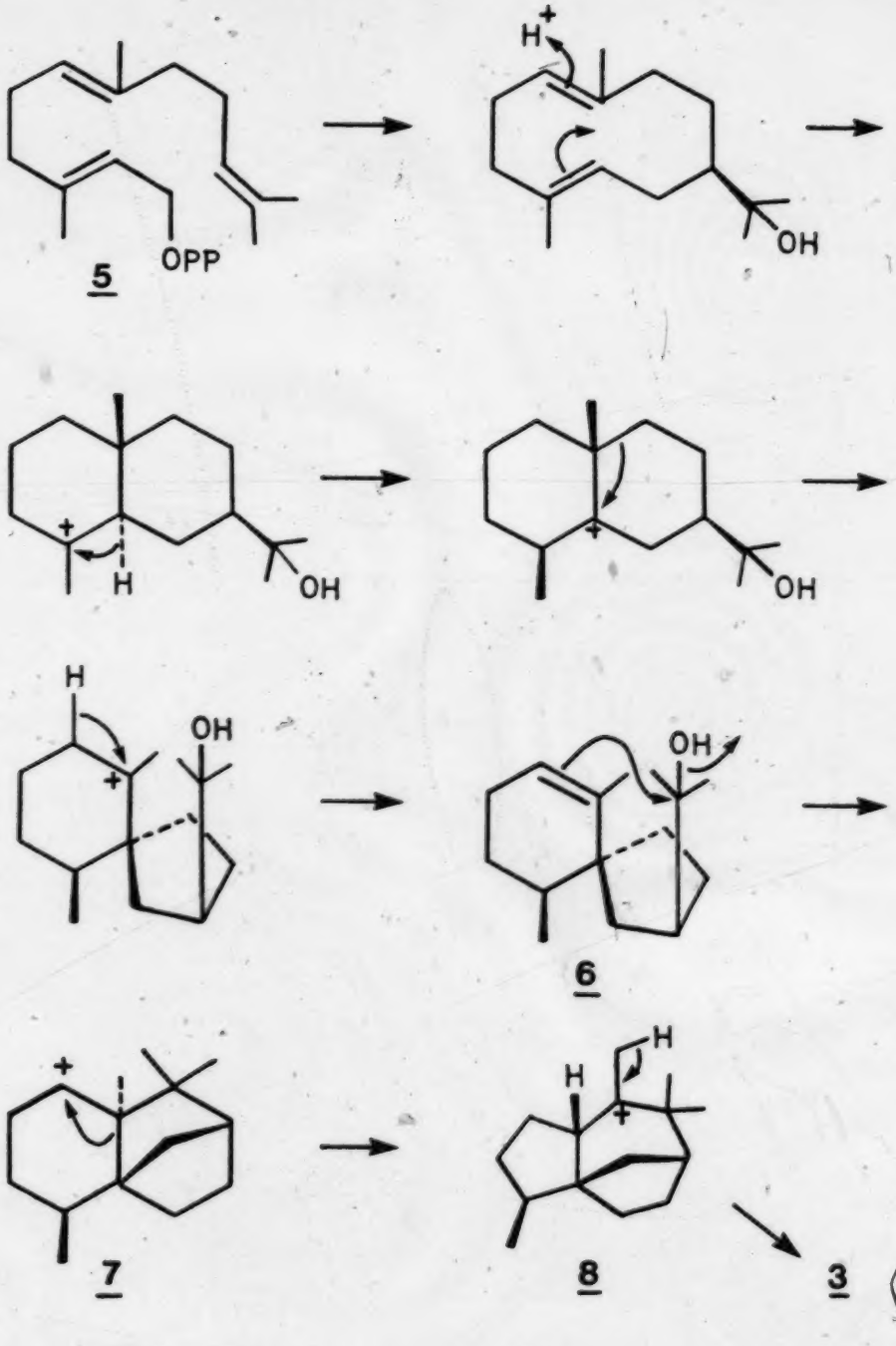
SCHEME I



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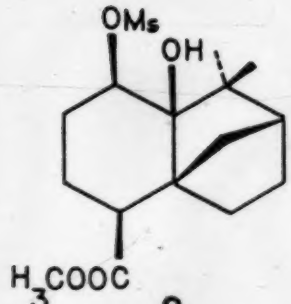

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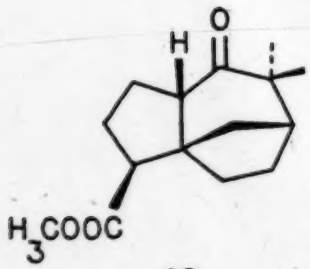

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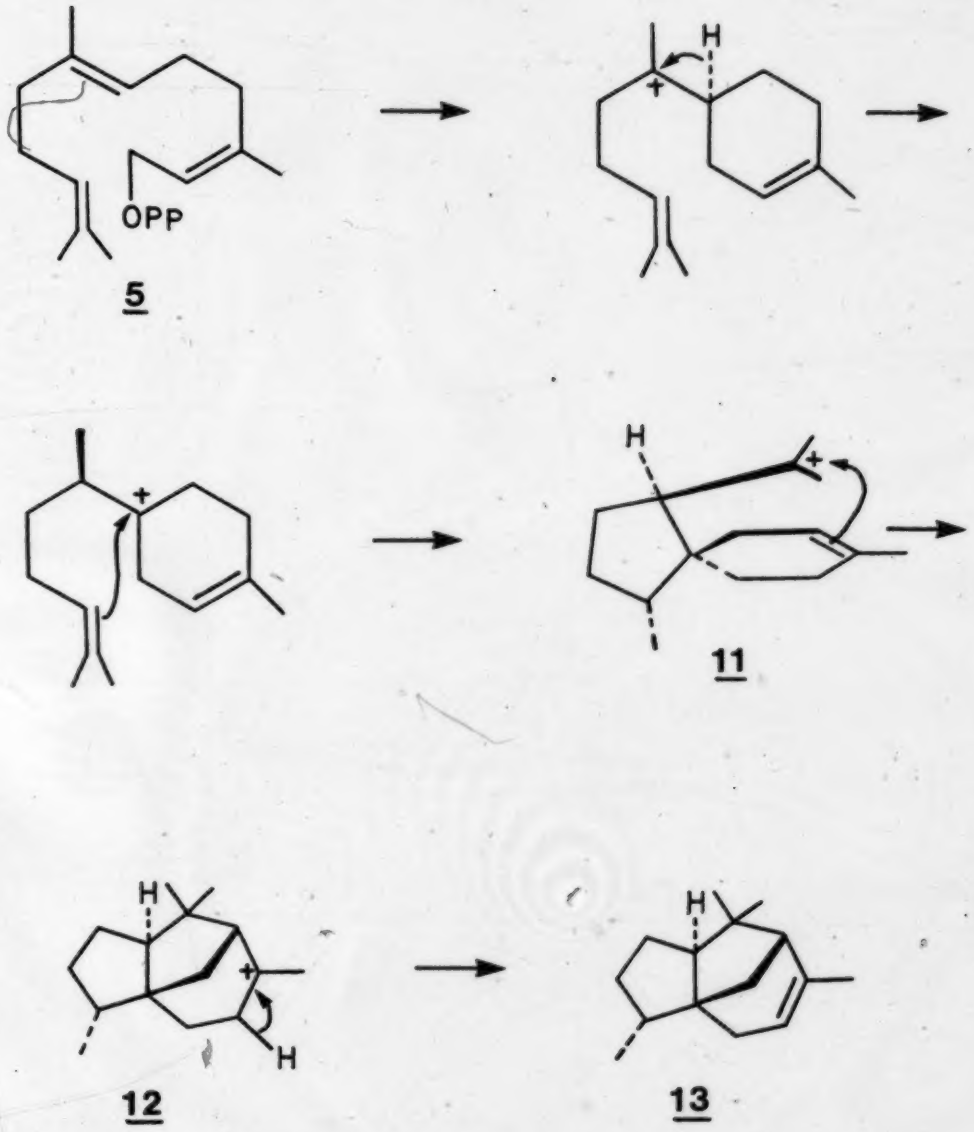

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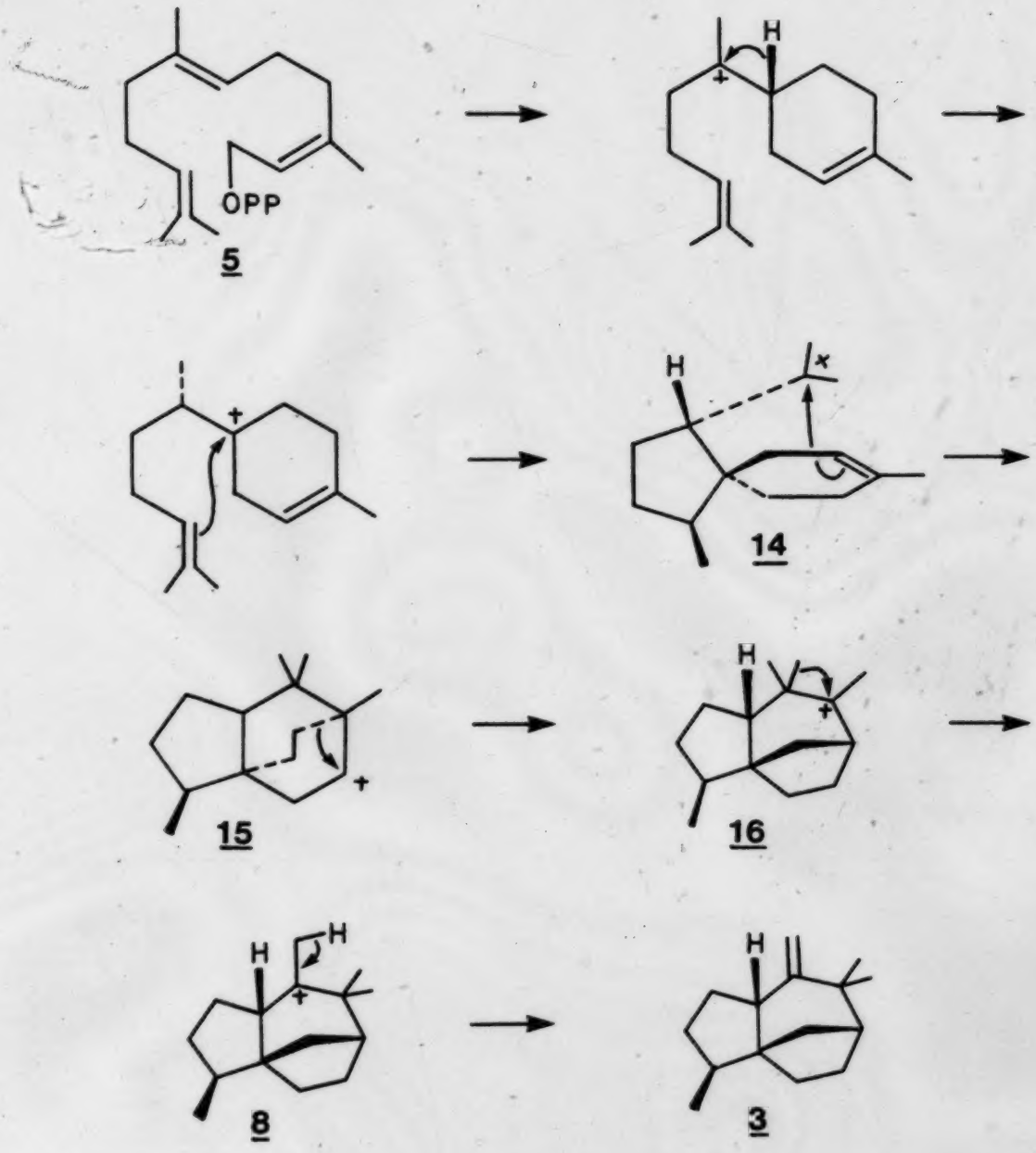

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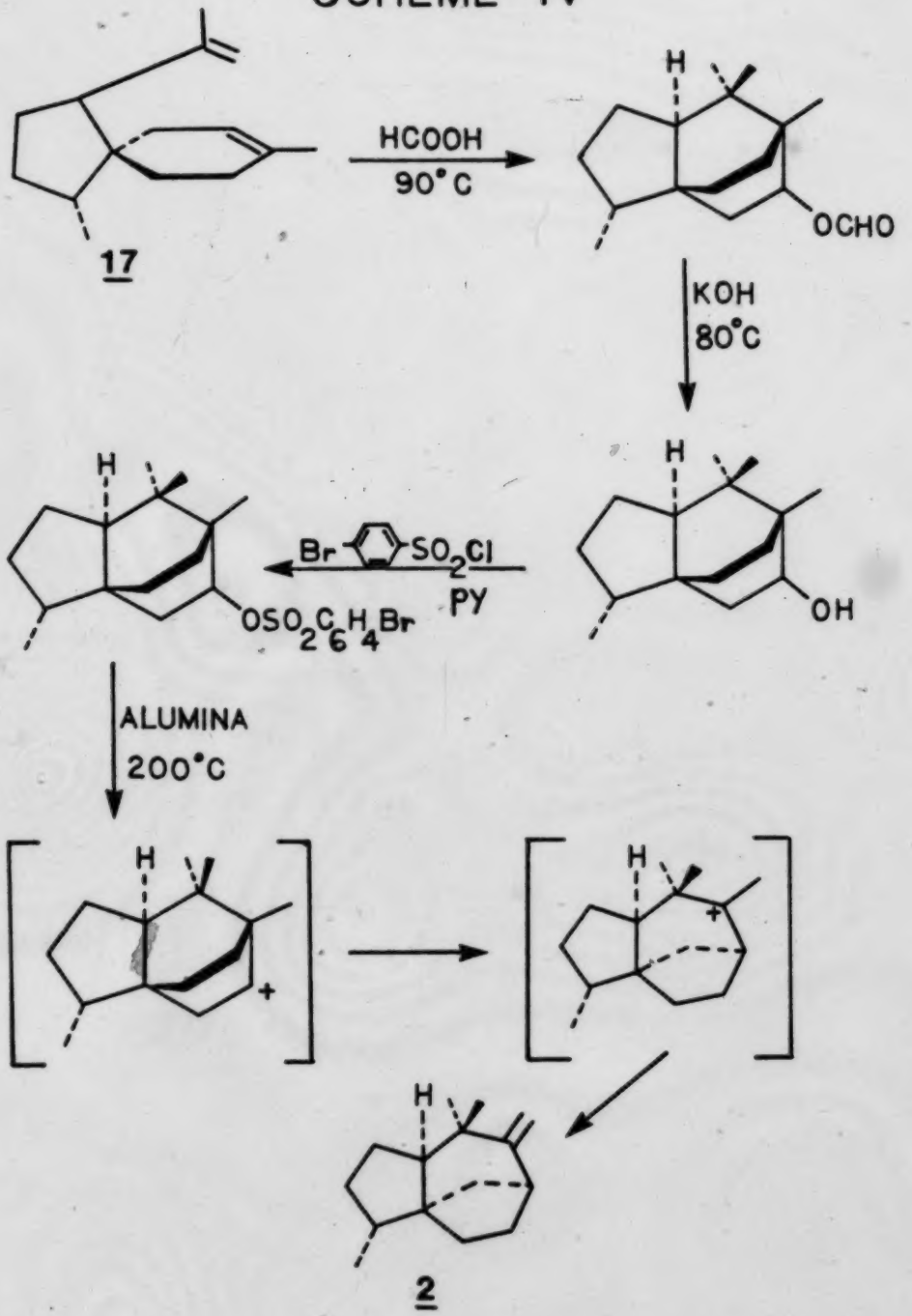

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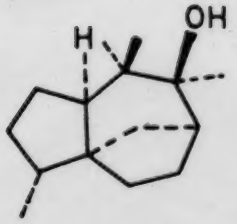

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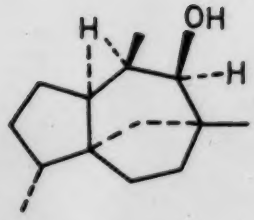

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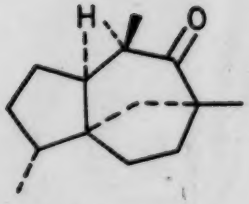

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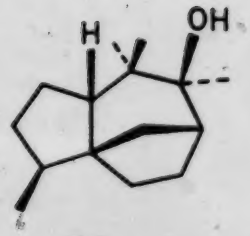

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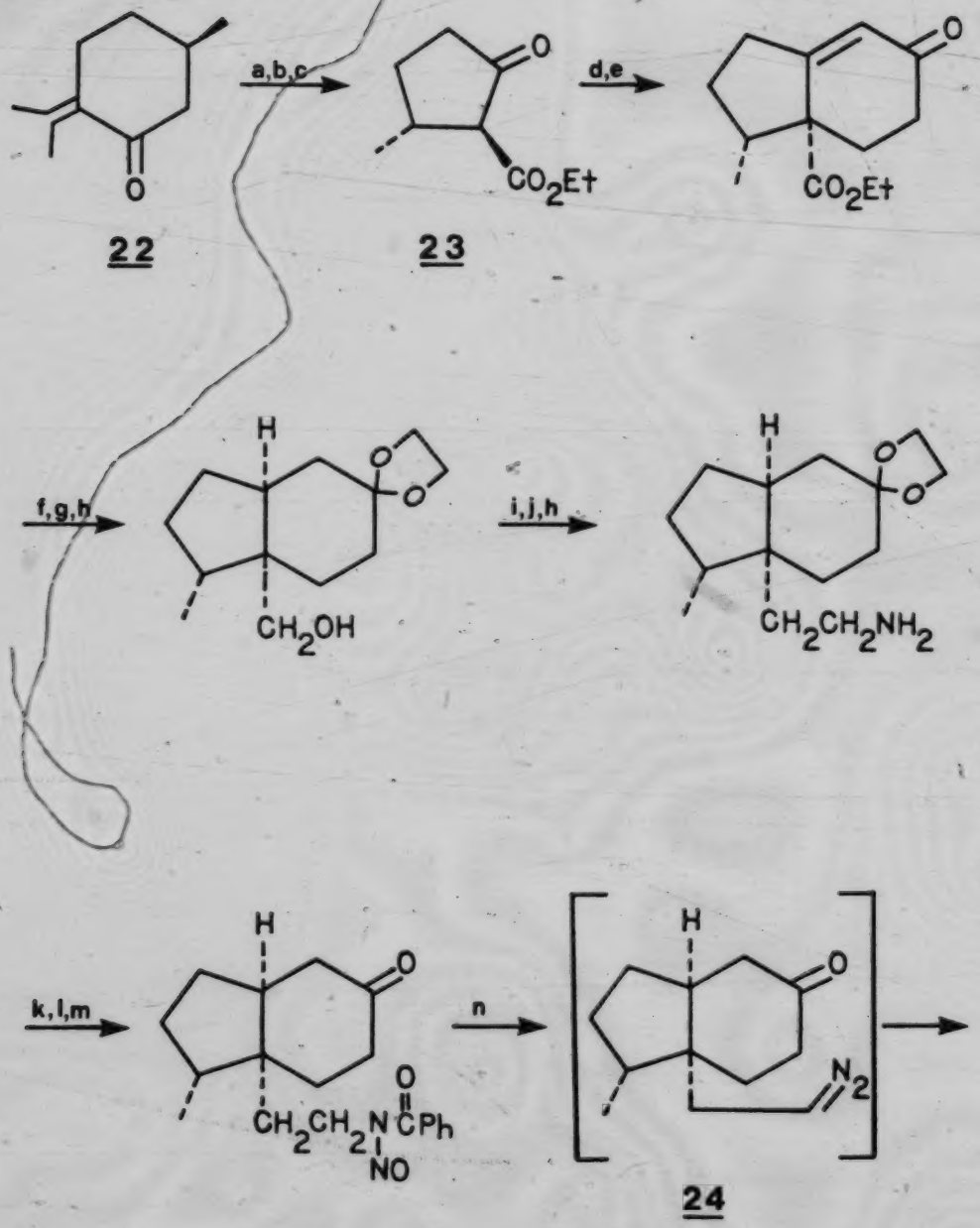
SCHEME V



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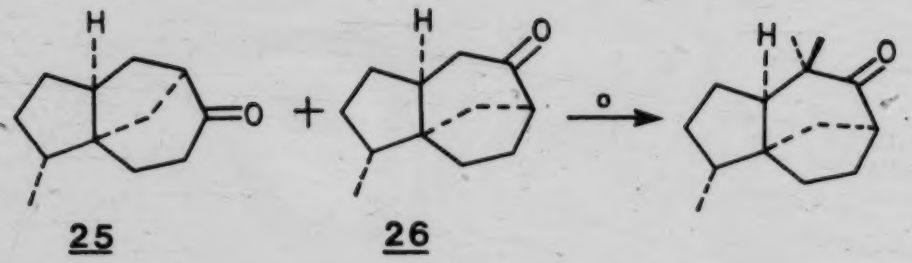

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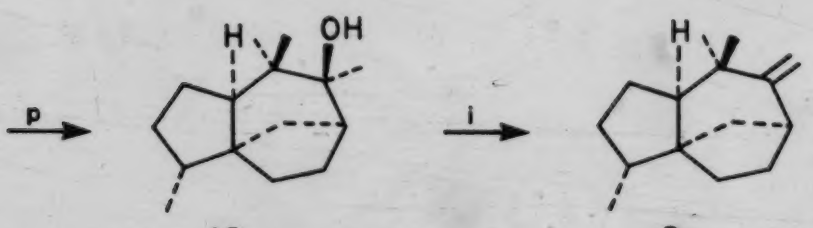
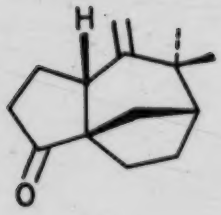


18 2

(a) Br_2, Et_2O. (b) NaOEt, Et_2O. (c) O_3. (d) MVK, Et_3N. (e) pyrrolidine, HOAc, H_2O. (f) H_2, Pd/C. (g) $(CH_2OH)_2$, H^+. (h) $LiAlH_4$. (i) CH_3SO_2Cl, Et_3N. (j) NaCN, Et_4NCl. (k) PhCOCl. (l) H_3O^+. (m) N_2O_4. (n) KOt-Bu, t-AmOH. (o) KH, CH_3I. (p) CH_3Li.



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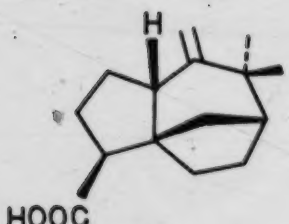

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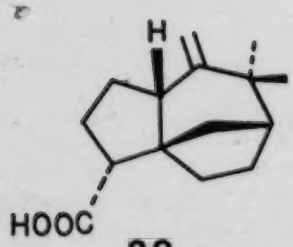

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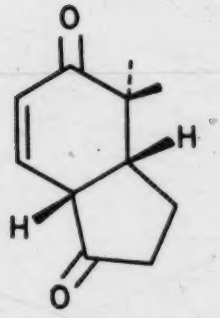

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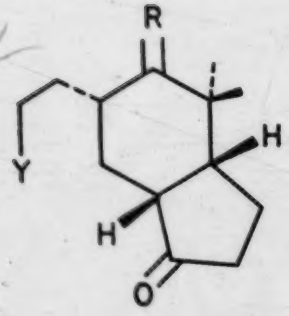

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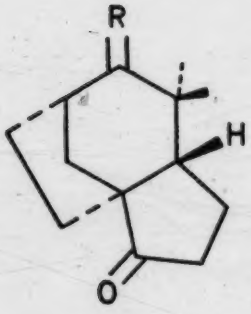

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CHAPTER II

RESULTS AND DISCUSSION

Our preliminary studies on the prezizanoid family focussed on the synthesis of the bicyclic diketone 31. The diketone 31 is an appropriate potential precursor of the prezizanoids possessing carbon skeleton 34. Not only does it contain the required fused bicyclic ring system, it also possesses suitable functionalities for further elaboration of the carbon framework as discussed previously.

By means of retrosynthetic analysis (Scheme VI), the desired diketone 31 can, in principle, be obtained from a 6,6-dimethyl-2-cyclohexenone derivative such as 35, possessing a functionalized three carbon side chain. The basic cyclohexenone skeleton can be envisaged as arising from a cyclopentene, e.g. 36, of the campholenic family, by a sequence involving ozonolysis and aldol condensation. Two logical compounds that could be used as starting materials are campholenic acid (37) and campholenic aldehyde (38), which can be easily obtained from 10-camphorsulfonic acid (39) (17) and α-pinene oxide (30) (18, 19) respectively.

Our initial synthetic route was designed to construct the cyclohexenone ring first, and then extend the C-5 side chain, forming an intermediate related to

35. To this end, commercially available d,l-10-camphorsulfonic acid (39) was fused with solid potassium hydroxide (17) to give α-campholenic acid (37) in 76% yield. The ir spectrum of the compound showed absorption bands characteristic of a carboxylic acid at 3200-2500 and 1709 cm^{-1}. The vinylic proton appeared as a complex multiplet at δ 5.24 in the nmr spectrum. The vinylic methyl was seen as a broad singlet at δ 1.62, while the geminal methyl groups were evident as sharp singlets at 1.02 and 0.80. Both the mass spectrum, which showed a molecular ion peak at 168.1147, and elemental analysis, were in agreement with the required molecular formula of $C_{10}H_{16}O_2$. Esterification of the acid 37 with potassium carbonate and methyl iodide in refluxing acetone (20) gave a 90% yield of methyl ester 40, which showed an ester absorption band in the ir spectrum at 1745 cm^{-1} and a singlet at δ 3.65 in the nmr spectrum for the three methoxy hydrogens.

The ester 40 was subjected to ozonolysis at -78°C in a solution of dichloromethane-methanol (1:1). Reductive workup using triphenylphosphine (21) afforded the intermediate keto aldehyde 41 which, due to its instability, was cyclized without purification, using p-toluenesulfonic acid in refluxing benzene with

continuous removal of water. The ir spectrum of the resulting keto ester 42, formed in 81% yield over the three steps, showed carbonyl absorption bands for an α,β-unsaturated ketone and an ester at 1677 and 1738 cm^{-1} respectively. The beta proton of the α,β-unsaturated ketone was displayed as a doublet of doublets of doublets centered at δ 6.80 (J = 10, J' = 5, and J" = 3 Hz) in the nmr spectrum. The alpha proton appeared at δ 5.94 as a triplet of doublets (J = 10 and J' = 2 Hz). The mass spectrum molecular ion peak at 196.1101 and elemental analysis confirmed the molecular formula $C_{11}H_{16}O_3$.

Reduction of keto ester 42 was attempted initially with lithium aluminum hydride in tetrahydrofuran. The reaction yielded two major products, one of which was the desired diol 43. The other displayed no vinylic protons in the nmr spectrum. Both hydroxy (3440 cm^{-1}) and saturated ketone carbonyl (1705 cm^{-1}) absorption bands appeared in the ir spectrum. Therefore, it was tentatively assigned the structure of the saturated keto alcohol 44. In an effort to improve upon these results, diisobutylaluminum hydride (DIBAL) (22) was used as the reducing agent. When the keto ester 42 was dissolved in ether and treated with DIBAL, the diol 43 was formed as the single major product in 73% yield.

The ir spectrum of compound 43 displayed a broad peak at 3340 cm^{-1}, indicative of the alcohol functionalities. In the nmr spectrum, the methylene group adjacent to the hydroxy on the side chain appeared as a multiplet at δ 3.70, whereas the methine proton adjacent to the ring hydroxyl group appeared as a broad singlet at δ 3.92. Oxidation of the diol 43 with an excess of pyridinium chlorochromate (23) in dichloromethane gave keto aldehyde 45 in 67% yield. The aldehydic proton appeared as a broad doublet (J = 2 Hz) in the nmr spectrum at δ 9.86. The ir spectrum showed aldehydic absorption bands at 2730 and 1735 cm^{-1} and an α,β-unsaturated ketone carbonyl stretch at 1680 cm^{-1}. A molecular ion peak at 166.0997 in the mass spectrum verified the $C_{10}H_{14}O_2$ molecular formula.

The extension of the side chain of aldehyde 45 by one carbon unit can conceivably be achieved by a Wittig reaction to form the vinyl ether 46, followed by hydrolysis to yield the aldehyde 47. Unfortunately, when the aldehyde 45 was treated with methoxymethylenetriphenylphosphorane, under various conditions, the reaction yielded a complex mixture of unidentifiable compounds. The failure to form 46 suggested that the α,β-unsaturated ketone might be undergoing 1,2 or 1,4 addition to the Wittig reagent. In order to circumvent

this problem, the protection of the ketone carbonyl prior to treatment with the Wittig reagent was attempted. Thus, the keto ester 42 was subjected to ketalization and thioketalization using standard conditions. However, the desired protection could not be achieved in either case. In the former reaction, the starting material was recovered, while in the latter case the major product exhibited no vinylic protons in the nmr spectrum. This suggested that Michael addition of the reagent, 1,2-ethanedithiol, to the conjugated enone, had occurred.

Since the extension of the side chain was difficult in the presence of the α,β-unsaturated ketone, a new synthetic strategy was explored. The succession of operations of our first route was reversed. The second pathway begins with the extension of the side chain of the campholenic precursor to the desired three carbons, followed by the formation of the cyclohexenone ring from the cyclopentene ring system. The starting material was again α-campholenic acid (37). The acid 37 was reduced to the alcohol 48 in 69% yield with lithium aluminum hydride in ether. The presence of a hydroxyl group was verified by the broad peak at 3321 cm^{-1} in the ir spectrum and the multiplet at δ 3.68 in the nmr spectrum, which represents the methylene group

adjacent to the hydroxyl group. Oxidation of the alcohol 48 to campholenic aldehyde (38) was accomplished using pyridinium chlorochromate in dichloromethane. The aldehyde 38, formed in 66% yield, showed characteristic absorption bands for an aldehyde in the ir spectrum at 2720 and 1727 cm^{-1}. The aldehydic proton appeared at δ 9.82 as a triplet (J = 2 Hz) in the nmr spectrum. The molecular formula of $C_{10}H_{16}O$ was verified by the molecular ion peak found at 152.1198 in the mass spectrum.

A more convenient route to campholenic aldehyde (38) involves the acid catalyzed ring opening of α-pinene oxide (30) (18, 19). Treatment of the commercially available epoxide 30 with freshly fused zinc chloride in refluxing benzene yields campholenic aldehyde (38) in 63% yield.

Extension of the side chain of aldehyde 38 by one carbon was affected by reaction with a Wittig reagent. The aldehyde 38 was treated with (methoxymethyl)-triphenylphosphonium chloride and sodium hydride in a solution of dimethyl sulfoxide and benzene (24, 25). The resulting vinyl ether 49, formed in 70% yield, was purified by distillation and flash chromatography. The nmr spectrum indicated the presence of both the cis and trans isomers of the vinyl ether 49. The methine

hydrogen adjacent to the methoxy group appeared as two multiplets, for both the cis and trans isomers, at δ 6.30 and 5.88, integrating for a total of one hydrogen. The other vinylic proton appeared as two multiplets at δ 4.72 and 4.36 for a total of one hydrogen. The methoxy group appears as two singlets at δ 3.58 and 3.50, integrating for a total of three hydrogens for the two isomers. The molecular ion peak in the mass spectrum at 180.1509 as well as elemental analysis, verified the $C_{12}H_{20}O$ molecular formula.

Usually, vinyl ethers are readily hydrolyzed to aldehydes or ketones under mild acidic conditions. In the present case, however, the hydrolysis of the vinyl ether 49 to the aldehyde 50 proved to be more difficult than had been anticipated. Treatment of the vinyl ether 49 with various acids, including perchloric, hydrochloric, nitric, acetic, trifluoroacetic, and oxalic, did not yield cleanly the desired aldehyde 50. Under these conditions, except in the case of acetic acid which gave no reaction, an alcoholic compound was formed in varying degrees as the main product. The ir spectrum of this compound revealed the absence of the carbonyl functionality required for the desired product 50. However, characteristic absorption bands for an alcohol (3390 cm^{-1}) and an exocyclic

double bond (1650 cm^{-1}) were present. The nmr spectrum contained a singlet at δ 4.88 integrating for two hydrogens, which is characteristic for an exocyclic double bond. The presence of a broad singlet at δ 2.70 and a multiplet at δ 3.66, each integrating for one hydrogen, was indicative of an alcoholic proton and a methine proton adjacent to a hydroxyl group. Evidence of geminal methyls appeared as two sharp singlets at δ 1.14 and 1.06, each representing three hydrogens. On the basis of the spectral data, the structure 51 was assigned to this compound. This assignment was further confirmed by the mass spectrum, which showed the required molecular ion peak at 166.1356. Formation of alcohol 51 was apparently a result of an intramolecular Prins reaction (26) of the intermediate aldehyde 50.

Although the Prins product 51 was inevitably formed in all the reactions attempted, under carefully controlled conditions it was possible to produce the desired aldehyde 50 in moderate yield. The best method involved treatment with 30% aqueous perchloric acid in ether at 0°C for a period of two to four minutes. The resulting aldehyde 50 was shown to be rather unstable. It readily converted to compound 51 on standing. Attempted purification of 50 by column chromatography on silica gel resulted in substantial loss of material.

However, a small amount of the pure aldehyde could be isolated by this method. The ir spectrum of the purified compound 50 showed absorption peaks at 2720 and 1710 cm^{-1}, characteristic of an aldehyde. The aldehydic proton appeared as a triplet (J = 2 Hz) at δ 9.80 in the nmr spectrum.

Due to the unsatisfactory reproducibility and yield of the acid hydrolysis of the vinyl ether 49, alternative methods for the preparation of aldehyde 50 were sought. In one case, the vinyl ether 49 was treated with trimethylsilyl iodide, generated *in situ* from trimethylsilyl chloride and sodium iodide, in refluxing acetonitrile (27). It was anticipated that the formation of the silyl enol ether would facilitate the production of the aldehyde 50. Unfortunately, the reaction was unsuccessful, forming a complex mixture of products.

Another method often used for the demethylation of aryl methyl ethers involves the use of thioethoxide in dimethylformamide (28, 29). When the vinyl ether 49 was treated with sodium hydride and ethanethiol in refluxing dimethylformamide, no reaction occurred and the starting material was recovered. On the other hand, when lithium hydride and thiophenol (1:1 in molar ratio) were used under the same conditions, the start-

ing material was consumed. However, the major product was found not to be the desired aldehyde 50, but the compound 52. The nmr spectrum of 52 indicated the presence of ten aromatic protons in the region of δ 7.00-7.60 and a single olefinic proton at δ 5.25 as a broad singlet. Mass spectrum verified the $C_{23}H_{28}S_2$ molecular formula of 52 displaying a molecular ion peak at 368.1631. Although this compound is most likely produced *via* the intermediacy of aldehyde 50, it remains unclear as to how the thioketalization occurred under basic conditions.

The decarboxylation of aliphatic glycidic acids has long been an established method (30) for the preparation of ketones and aldehydes. With this in mind, we chose to prepare the glycidic acid 54, which should thermally decarboxylate to form aldehyde 50. The glycidic acid 54 was prepared from the corresponding ester 53, which was obtained from aldehyde 38 by a modified Darzens reaction. The aldehyde 38 was treated with lithium bis(trimethylsilyl)amide and ethylbromoacetate in tetrahydrofuran (31) to produce the glycidic ester 53 in 54% yield (based on consumed starting material). The ir spectrum of 53 showed the characteristic ester absorption band at 1760 cm^{-1}, as well as an olefinic band at 1680 cm^{-1}. The nmr

spectrum correlated well with the assigned structure. The epoxy protons appeared as two multiplets at δ 3.52 and 3.20. The methylene hydrogens of the ethoxy group were seen as a quartet (J = 7 Hz) at δ 4.25, while the methyl hydrogens of that group appeared as a triplet (J = 7 Hz) at δ 1.30. The mass spectrum displayed a molecular ion peak at 238.1560, verifying the $C_{14}H_{22}O_3$ molecular formula. The ester 53 was subsequently hydrolyzed with aqueous sodium hydroxide in 98% ethanol to give the sodium salt of the glycidic acid 54. The salt, after acidic workup, yielded the glycidic acid 54 in 78% yield. That the ethoxy group was removed and that an acid had been formed were evident from the absence of the ethoxy signals and the appearance of a broad singlet at δ 9.35 due to the acidic proton in the nmr spectrum. The glycidic acid 54 was subjected to pyrolysis at 150°C/5 torr for ten hours. Although decomposition of the compound 54 was found to be complete, only traces of the desired aldehyde 50 were produced.

Prior to further discussion, a brief summary of results is deemed appropriate. Campholenic aldehyde (38) has been prepared both by a three-step synthesis from 10-camphorsulfonic acid (39) and directly from α-pinene oxide (30). Wittig reaction of 38 yielded the

vinyl ether 49, which was hydrolyzed by means of 30% perchloric acid to the aldehyde 50.

In order to form the cyclohexenone ring system, aldehyde 50 was subjected to ozonolysis. The expected product, keto aldehyde 55, could theoretically undergo selective aldol condensation to give the desired compound 47. However, ozonolysis of aldehyde 50 could not be carried out successfully using either dichloromethane or methanol-dichloromethane (1:1) as a solvent system. The former gave a complex mixture, whereas the latter afforded mainly compound 56. Its structure was assigned on the basis of the nmr spectrum displaying three methyl singlets at δ 0.92, 0.94 and 1.25, two methoxy singlets at δ 3.25 and 3.45, a multiplet at δ 9.70 for the aldehydic proton and a doublet of doublets at δ 4.48 (J = 10 and J' = 4 Hz) for the methine proton geminal to the methoxy group. Equally unsuccessful was the attempted hydrolysis of compound 56 with hydrochloric acid in ether. Instead of the desired keto aldehyde 55, the reaction gave a complex mixture of unidentifiable compounds.

The transformation of the cyclopentene ring, present in compound 50, to a cyclohexenone ring system was found to be difficult, presumably due to the presence of the aldehyde functionality. Modification

of this labile functional group to form an ester, via a carboxylic acid, was deemed appropriate. A standard method for the oxidation of an aldehyde to an acid is reaction with Jones reagent (32). However, since aldehyde 50 is particularly susceptible to Prins reaction under acidic conditions, this method was not used. The use of Tollen's reagent, a basic oxidizing reagent, was preferred.

Since the aldehyde 50 was shown to be unstable, it was more practical to carry out the oxidation on the crude material, obtained directly from the hydrolysis of vinyl ether 49 (vide supra). Treatment of this material with Tollen's reagent in 98% ethanol gave the acid 57 in 39% yield from vinyl ether 49. The structure of 57 was verified by the ir spectrum, which contained the characteristic acid bands at 3300-2700 and 1710 cm^{-1}. Both the mass spectrum, which gave a molecular ion peak of 182.1308, and elemental analysis agreed with a molecular formula of $C_{11}H_{18}O_2$.

Esterification of acid 57 with potassium carbonate and methyl iodide in refluxing acetone afforded the ester 58 in 60% yield. The ester carbonyl stretch appeared at 1742 cm^{-1} in the ir spectrum and the methoxy hydrogens were observed as a sharp singlet at δ 3.68 in the nmr spectrum.

Although the conversion of aldehyde 50 to ester 58 could be successfully carried out, further transformation of ester 58 was not pursued in light of complications encountered in the hydrolysis of vinyl ether 49. Instead, at this point, we chose to explore the possible use of compound 49 in a different manner. The new direction takes advantage of the expected difference in reactivity of its two double bonds towards catalytic hydrogenation. Selective hydrogenation is expected to saturate only the side chain double bond, forming a stable methyl ether moiety which should not interfere with the operations required to modify the ring system, and whose oxidation level could be appropriately adjusted at a later stage. Towards this end, vinyl ether 49 was subjected to hydrogenation with 5% palladium on carbon in ethyl acetate, at room temperature and atmospheric pressure. The selective hydrogenation of the side chain double bond indeed occurred to give the ether 59, but the reaction also produced a substantial amount of alcohol 51, resulting from the hydrolysis of the starting material and subsequent cyclization. The formation of this undesired byproduct could be completely eliminated when the hydrogenation was carried out in the presence of one equivalent of potassium acetate, using glassware

prewashed with ammonium hydroxide. Under these conditions, the desired ether 59 was formed cleanly in high yield (97%). The ir spectrum of 59 displayed characteristic absorption bands for an olefin (1645 cm^{-1}) and an ether (1122 cm^{-1}). In the nmr spectrum, a single vinylic proton was displayed at δ 5.24 as a broad singlet, and the five hydrogens surrounding the ether oxygen appeared as a multiplet at δ 3.40.

Ozonolysis of ether 59 in a mixture of dichloromethane and methanol (1:1) at -78°C, followed by reductive workup with zinc dust and glacial acetic acid (33) afforded the unstable keto aldehyde 60. This compound, without purification, was subjected to cyclization using p-toluenesulfonic acid in refluxing benzene to give keto ether 61 in 56% yield from ether 59. The ir spectrum showed an α,β-unsaturated ketone absorption band at 1675 cm^{-1} and an ether band at 1118 cm^{-1}. The presence of a conjugated enone system was further verified by the nmr spectrum. The alpha proton appeared as a triplet of doublets (J = 10 and J' = 2 Hz) at δ 5.94 and the beta proton appeared at δ 6.84 as a doublet of doublets of doublets (J = 10, J' = 5 and J" = 3Hz). The ether hydrogens appeared in an identical manner to those in 59, and the geminal methyls were evident as singlets at δ 1.18 and 1.00. Both the mass spectrum, with a molecular ion peak of 196.1462,

and elemental analysis agreed with a molecular formula of $C_{12}H_{20}O_2$.

At this point, with the goal of the bicyclic ketone 31 in mind, it was necessary to modify the side chain of keto ether 61 to provide a suitable substrate for cyclization. Therefore, the conversion of the methyl ether 61 to the alcohol 62 was undertaken. Recent reports described trimethylsilyl iodide as an excellent reagent for the demethylation of methyl ethers to alcohols (27, 34). Accordingly, compound 61 was treated with trimethylsilyl iodide in chloroform (34) at room temperature. To our disappointment, the starting material was recovered intact. However, when trimethylsilyl iodide was generated *in situ*, from trimethylsilyl chloride and sodium iodide, and when the reaction was performed in acetonitrile (27), the methyl ether 61 was completely consumed within sixteen hours. Contrary to our expectations, the major product, obtained in *ca.* 30% yield, was found not to be the alcohol 62, but the corresponding iodo compound 63, which showed absorption bands for an alkyl halide (1240 cm^{-1}) and an α,β-unsaturated ketone (1674 cm^{-1}) in the ir spectrum. The mass spectrum had a molecular ion peak of 292.0319, confirming the molecular formula $C_{11}H_{17}OI$.

An alternative reagent which is known to be highly effective for demethylation of a methyl ether is boron tribromide (35). Thus, keto ether 61 was treated with boron tribromide in dichloromethane at room temperature. However, the single product formed in 78% yield was shown again not to be the desired alcohol 62, but the bromide 64, which showed no hydroxy absorption bands in the ir spectrum. The ether protons of the starting material were absent from the nmr spectrum of 64. Instead, a triplet (J = 6 Hz), appearing at δ 3.44, strongly indicated the presence of a methylene group adjacent to a bromine atom. The mass spectrum had characteristic molecular ion peaks at 244.0464 and 246.0445, verifying the molecular formula of $C_{11}H_{17}OBr$.

In light of literature precedence (27, 34, 35) that methyl ethers undergo reaction with both trimethylsilyl iodide and boron tribromide to give alcohols, the above results were most unusual. The unexpected halide formation could be rationalized by invoking the participation of the neighboring ketone carbonyl (65 → 66), as shown in Scheme VII with boron tribromide.

Regardless of the exact cause of the formation of halides 63 and 64, the fact that the desired alcohol 62 could not be obtained directly from methyl ether 61

propounded its preparation indirectly via these compounds. Since the bromide 64 was obtained in much higher yield than the iodide 63, it was used for subsequent transformations.

Attempted hydrolysis of the bromide 64 to alcohol 62 by treatment with potassium hydroxide in tetrahydrofuran at room temperature was unsuccessful and resulted only in recovery of starting material. On the other hand, when the reaction was carried out at refluxing temperature, alcohol 62 was formed in poor yield, along with several unidentified products. A more successful method for the desired transformation involved the treatment of bromide 64 with silver carbonate (36) in aqueous tetrahydrofuran, at 50°C, for four days. In this way, alcohol 62 was obtained in 53% yield. The characteristic alcohol absorption peak appeared at 3430 cm^{-1} in the ir spectrum. A molecular ion peak of 182.1307 in the mass spectrum verified the molecular formula $C_{11}H_{18}O_2$.

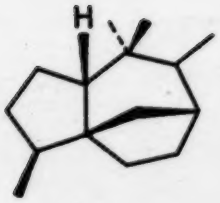
For the cyclization leading to the target molecule 31, several suitable intermediates were prepared from the alcohol 62. Treatment of alcohol 62 with pyridinium chlorochromate in dichloromethane at room temperature gave the corresponding aldehyde 47 in 96% yield. The ir spectrum of 47 displayed characteristic

aldehyde absorption bands at 2720 and 1723 cm^{-1}. The aldehydic proton appeared in the nmr spectrum as a triplet (J = 1 Hz) at δ 9.78. The mass spectrum contained a molecular ion peak at 180.1150, verifying the $C_{11}H_{16}O_2$ molecular formula. The alcohol 62 was also directly oxidized to the carboxylic acid 67 in 96% yield with Jones reagent in acetone at 0°C. The ir spectrum of this compound displayed absorption bands at 3200-2800 and 1709 cm^{-1}, characteristic for an acid. The acidic proton appeared at δ 8.90 in the nmr spectrum as a broad singlet. Esterification of acid 67 with potassium carbonate and methyl iodide in refluxing acetone resulted in the formation of ester 68 in 69% yield. The ester functional group was expressed at 1738 cm^{-1} in the ir spectrum. The methoxy group appeared as a singlet in the nmr spectrum at δ 3.68. The mass spectrum, displaying a molecular ion peak at 210.1257, verified the $C_{12}H_{18}O_3$ molecular formula.

These compounds, each possessing a suitable side chain, are expected to undergo facile cyclization. However, at the present time, we have not been able to carry out this transformation, although several attempts have been made as follows. Aldehyde 47 and ester 68 were individually treated with sodium hydride in 1,2-dimethoxyethane. These reactions resulted in

substantial loss of material, and in each case, the desired product was not detected. Ester 68 was also subjected to treatment with pyrrolidine in refluxing benzene, in an attempt to induce cyclization *via* an enamine intermediate. This was found to be unsuccessful, resulting in complete recovery of starting material. In the case of the carboxylic acid 67, cyclization was attempted by treatment with boron trifluoride etherate in acetic acid, in the presence of acetic anhydride (37), either at room temperature or at reflux. In both cases, the starting material was recovered intact.

Suitable conditions which would effect the desired cyclization are being further studied. We are confident that the preparation of the projected key intermediate 31 can be achieved *via* the potential intermediates 47, 67, and 68 so far obtained.



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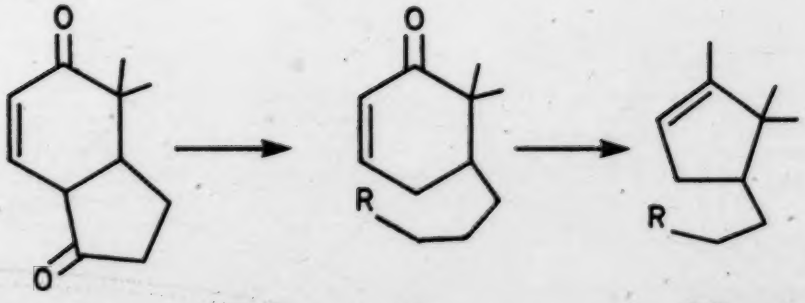
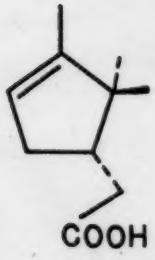


31 35 36

SCHEME VI



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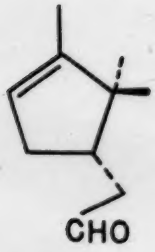

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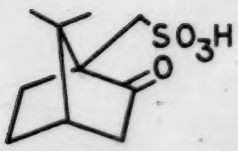

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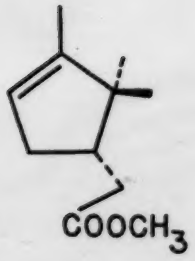

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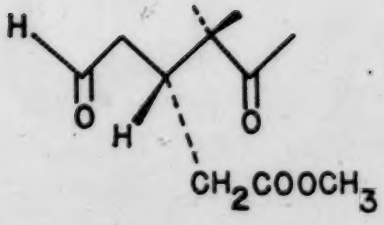

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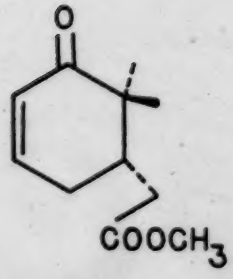

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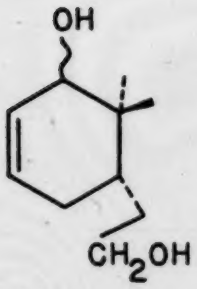

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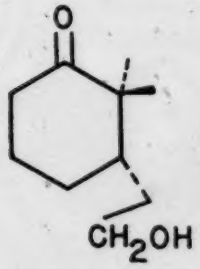

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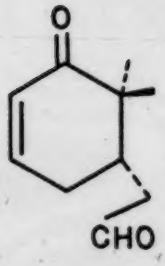

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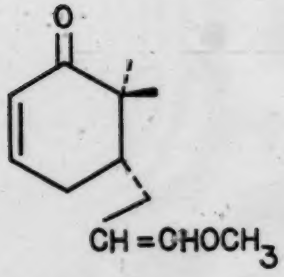

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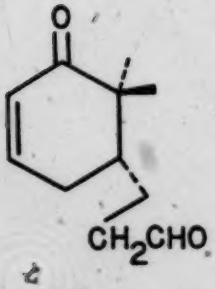

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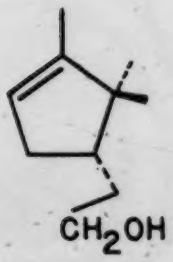

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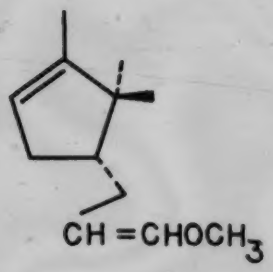

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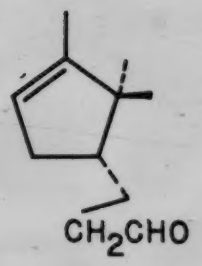

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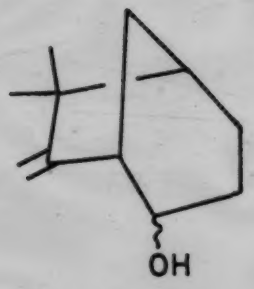

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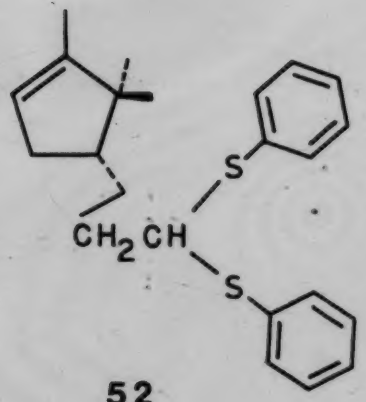

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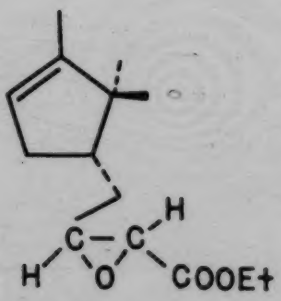

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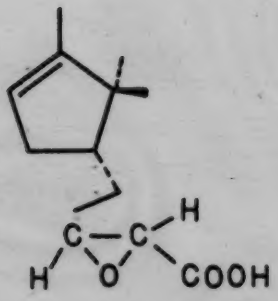

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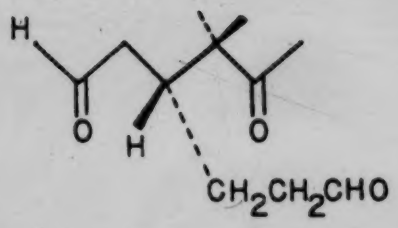
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H
O
CH2CH2CHO

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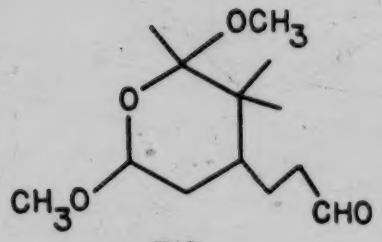
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O
CH3O
CHO

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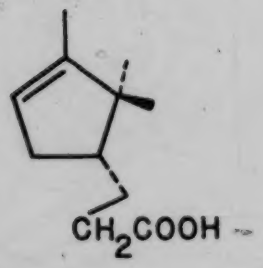
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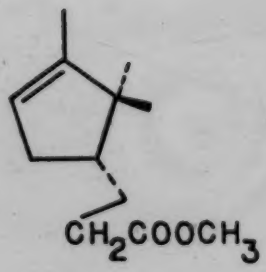
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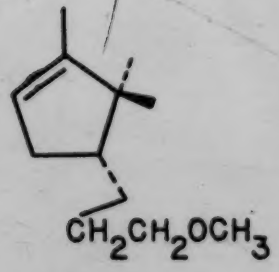
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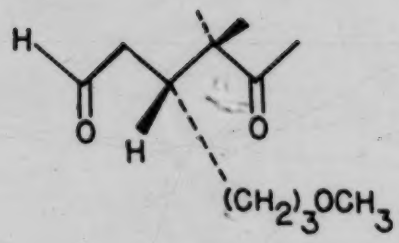

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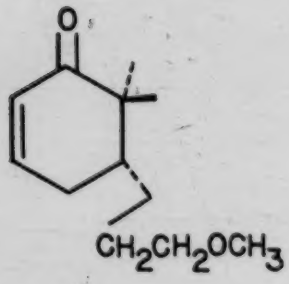

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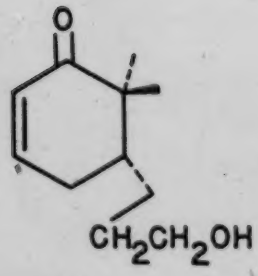

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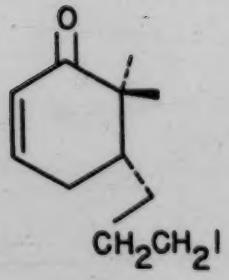

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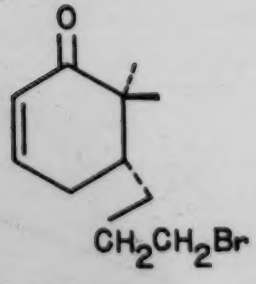

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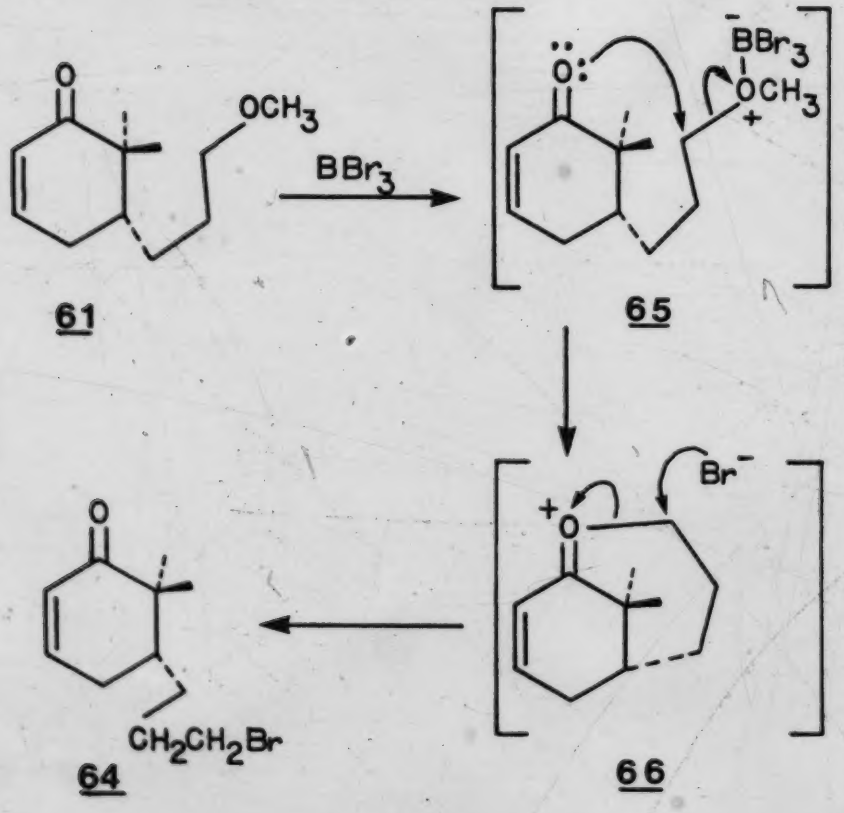
SCHEME VII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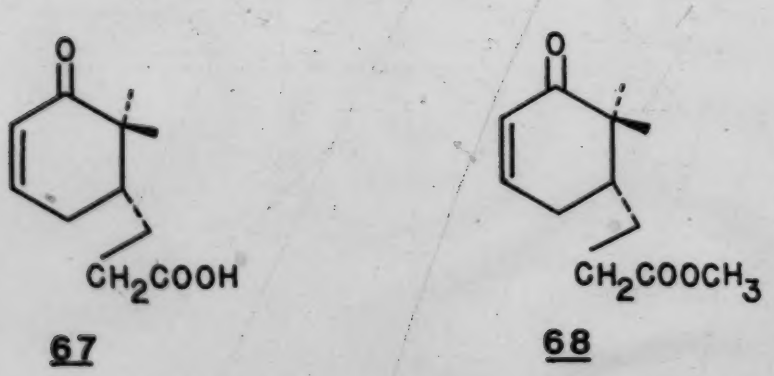
BBr3
OCH3
+
61
65
Br⁻
+O
O
CH2CH2Br
64
66


O
CH2COOH
67
O
CH2COOCH3
68

CHAPTER III

EXPERIMENTAL

General

Infrared (ir) spectra were obtained by using Perkin-Elmer Model 457 and Nicolet 7199 FT-IR spectrophotometers. Unless otherwise stated, ir samples were run as thin films. Proton nuclear magnetic resonance (nmr) spectra were recorded on Bruker WP-80 and Varian HA-100/Digilab HFT spectrometers. Deuterated chloroform was employed as the solvent and tetramethylsilane as internal standard. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Mass spectra (ms) were recorded using A.E.I. Model MS50 mass spectrometer. Elemental analyses were performed by the microanalytical laboratory of this department.

Materials

Benzene, diethyl ether (ether), tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) used for reactions were freshly distilled from lithium aluminum hydride. Methanol and ethanol were refluxed over magnesium turnings at elevated temperature for 2 hr. and distilled. Dimethyl sulfoxide (DMSO) and acetonitrile

were distilled from calcium hydride. Acetone was treated with potassium permanganate and distilled. Dichloromethane was washed with aqueous 5% sodium carbonate solution, dried over calcium chloride and distilled. N,N-Dimethylformamide (DMF) was distilled over phosphorus pentoxide. d,l-10-Camphorsulfonic acid and α-pinene oxide were obtained from Aldrich Chemical Company. Ozone was generated with a Welsbach ozonator. Nitrogen and argon were passed through a purification sequence of Fieser's solution, concentrated sulfuric acid and potassium hydroxide pellets. Silica gel, 0.040-0.063 mm particle size, 230-400 mesh ASTM was used as adsorbent for flash chromatography (38), and silica gel 60-120 mesh was used as adsorbent for column chromatography. Thin layer chromatography was carried out using Merck silica gel G.

α-Campholenic acid (37)

To fused potassium hydroxide (85%, 120 g, 1.82 mol) in a large porcelain casserole, was added, slowly with stirring, d,l-10-camphorsulfonic acid (39) (98%, 93.0 g, 0.39 mol). After the addition was complete, heating was continued for ten minutes. Upon cooling, the dark brown molten mass was dissolved in ice water (500 ml). The aqueous solution was washed with ether

(4 x 100 ml), acidified with ice-cold dilute hydrochloric acid, and extracted with ether (5 x 200 ml). The organic solution was washed with saturated sodium chloride solution and water, dried (magnesium sulfate), filtered and concentrated. The residue was distilled to give pure acid 37 (50.1 g, 76% yield): b.p. 89°C/0.3 torr; ir 3200-2500 and 1709 cm^{-1} (acid); nmr δ 10.88 (br. s, 1H, -COOH), 5.24 (m, 1H, -HC=), 1.62 (br. s, 3H, CH_3-CH=), 1.02 (s, 3H, $-CH_3$), and 0.80 (s, 3H, $-CH_3$); ms M^+ 168.1147 (calcd. for $C_{10}H_{16}O_2$: 168.1150). Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59; Found: C, 71.36; H, 9.58.

Methyl-α-campholenate (40)

A mixture of α-campholenic acid 37 (47 g, 0.28 mol) and anhydrous potassium carbonate (95 g, 0.69 mol) in acetone (460 ml) was stirred at room temperature for two hours. Methyl iodide (76 ml, 1.23 mol) was added and the reaction mixture refluxed overnight. After most of the acetone and excess methyl iodide was removed by distillation, water was added and the product extracted with dichloromethane (4 x 100 ml). The organic solution was dried (sodium sulfate), filtered and concentrated. Bulb-to-bulb distillation (80°C/0.9 torr) gave the methyl ester 40 (46.1 g, 90% yield): ir 1745

cm^{-1} (ester); nmr δ 5.23 (br. s, 1H, -CH=), 3.65 (s, 3H, $-COOCH_3$), 1.60 (m, 3H, $CH_3\overset{|}{C}=$), 1.00 (s, 3H, $-CH_3$), and 0.78 (s, 3H, $-CH_3$); ms M^+ 182.1308 (calcd. for $C_{11}H_{18}O_2$: 182.1307).

5-Carbomethoxymethyl-6,6-dimethyl-2-cyclohexenone (42)

At -78°C, ozone (condition: E = 80V, air inlet = 8 psi, ozone outlet = 0.06 psi) was allowed to pass through a solution of the methyl ester 40 (43.94 g, 0.24 mol) in methanol (110 ml) and dichloromethane (135 ml) until a light blue color was retained (about 7.5 hours). Triphenylphosphine (63 g, 0.24 mol) was added to the solution under a nitrogen atmosphere. The mixture was allowed to warm to room temperature and stirred overnight. After removal of the solvent, the crude keto aldehyde 41, without purification, was dissolved in benzene (200 ml). p-Toluenesulfonic acid (4.82 g, 0.028 mol) was added and the mixture refluxed for seven hours with continuous removal of water using a Dean-Stark water separator. After removal of the solvent, ether was added to precipitate triphenylphosphine oxide. After filtering and concentrating, the residue was distilled at 100°C/2 torr using a Kugelrohr apparatus to give the enone ester 42 (37.90 g, 81% yield): ir 1677 (α,β-unsaturated ketone) and

1738 cm^{-1} (ester); nmr δ 6.80 (ddd, 1H, J = 10, J' = 5, and J" = 3 Hz, -COCH=CH-), 5.94 (td, 1H, J = 10, and J' = 2 Hz, -COCH=CH-), 3.68 (s, 3H, $-COOCH_3$), 1.18 (s, 3H, $-CH_3$), and 1.00 (s, 3H, $-CH_3$); ms M^+ 196.1101 (calcd. for $C_{11}H_{16}O_3$: 196.1100).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.31; H, 8.22; Found: C, 67.34; H, 8.35.

5-(2-Hydroxyethyl)-6,6-dimethyl-2-cyclohexen-1-ol (43)

At 0°C, a 75% solution of diisobutylaluminum hydride in toluene (32 ml, 47.31 mmol) was added to a solution of the keto ester 42 (2.041 g, 10.41 mmol) in ether (10 ml) under an argon atmosphere. After thirty minutes, the reaction mixture was allowed to come to room temperature and stirred for an additional ninety minutes. Water (20 ml) was added and the mixture filtered to remove aluminum hydroxide. The filtrate was extracted with dichloromethane (4 x 40 ml). The organic solution was dried (magnesium sulfate), filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 30% ethyl acetate in petroleum ether, gave the diol 43 (1.30 g, 73% yield): ir ($CHCl_3$) 3340 (alcohol), 3020 and 1660 cm^{-1} (olefin); nmr δ 5.66 (m, 2H, -CH=CH-), 3.92 (br. s, 1H, -CHOH), 3.70 (m, 2H, $-CH_2OH$), 1.90 (br. s, 2H,

-OH), 1.04 (s, 3H, $-CH_3$), and 0.74 (s, 3H, $-CH_3$); ms M^+ 170.1307 (calcd. for $C_{10}H_{18}O_2$: 170.1307).

6,6-Dimethyl-5-(2-oxoethyl)-2-cyclohexenone (45)

To a suspension of pyridinium chlorochromate (1.040 g, 4.84 mmol) in dichloromethane (25 ml), was introduced a solution of the diol 43 (205 mg, 1.21 mmol) in dichloromethane (10 ml). The mixture was stirred for two hours at room temperature under an argon atmosphere. Ether (20 ml) was added and the mixture filtered through a short pad of florisil. After removal of the solvent, the product was purified by column chromatography on silica gel, using 10% ethyl acetate in petroleum ether. The pure keto aldehyde 45 (134 mg, 67% yield) gave the following spectral data: ir 2730, 1735 (aldehyde) and 1680 cm^{-1} (α,β-unsaturated ketone); nmr δ 9.86 (br. d, 1H, J = 2 Hz, -CHO), 6.86 (ddd, 1H, J = 10, J' = 5, and J" = 3 Hz, $-COCH=C\underline{H}-$), 6.02 (td, 1H, J = 10 and J' = 2 Hz, $-COC\underline{H}=CH-$), 1.20 (s, 3H, $-CH_3$), and 1.04 (s, 3H, $-CH_3$); ms M^+ 166.0997 (calcd. for $C_{10}H_{14}O_2$: 166.0994).

2-(2,2,3-Trimethyl-3-cyclopentenyl)ethanol (48)

To a suspension of lithium aluminum hydride (185 mg, 4.87 mmol) in ether (10 ml), at 0°C, α-campholenic

acid (37) (450 mg, 2.68 mmol) in ether (5 ml) was added dropwise. The mixture was allowed to come to room temperature and stirred for two hours. After cooling to 0°C, the mixture was successively treated with water (2 ml), aqueous 3N sodium hydroxide (2 ml) and water (2 ml). The aluminum hydroxide was filtered off. The filtrate was dried (magnesium sulfate), filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 30% ether in petroleum ether, afforded the alcohol 48 (287 mg, 69% yield); ir 3321 (alcohol) and 1670 cm^{-1} (olefin); nmr δ 5.24 (br. s, 1H, -HC=), 3.68 (m, 2H, $-CH_2OH$), 1.62 (m, 3H, $CH_3\overset{|}{C}=$), 1.00 (s, 3H, $-CH_3$), and 0.80 (s, 3H, $-CH_3$); ms M^+ 154.1356 (calcd. for $C_{10}H_{18}O$: 154.1358).

α-Campholenic aldehyde (38)

From alcohol 48

To a suspension of pyridinium chlorochromate (17.87 g, 83.12 mmol) in dichloromethane (100 ml), a solution of the alcohol 48 (3.20 g, 20.78 mmol) in dichloromethane (50 ml) was introduced. The mixture was stirred at room temperature under an argon atmosphere for three hours. Ether (50 ml) was added and the mixture filtered through a short pad of florisil. After removal of the solvent, the product

was purified by flash chromatography on silica gel, using 2% ether in petroleum ether. The pure aldehyde 38 (2.10 g, 66% yield) gave the following spectral data: ir 2720 and 1727 (aldehyde) and 1650 cm^{-1} (olefin); nmr δ 9.82 (t, 1H, J = 2 Hz, -CHO), 5.26 (br. s, 1H, -HC=), 1.62 (m, 3H, CH_3C=), 1.02 (s, 3H, $-CH_3$), 0.80 (s, 3H, $-CH_3$); ms M^+ 152.1198 (calcd. for $C_{10}H_{16}O$: 152.1201).

From α-pinene oxide (30)

α-Pinene oxide (30) (95%, 19.50 g, 0.12 mol) was added to freshly fused zinc chloride (275 mg, 0.002 mol) in benzene (50 ml). The mixture was refluxed for five hours. After the solvent was removed, the residue was distilled at 65°C/4.5 torr to give the aldehyde 38 (11.70 g, 63% yield).

1-Methoxy-3-(2,2,3-trimethyl-3-cyclopentenyl)propene (49)

A mixture of sodium hydride (1.55 g of 50% dispersion in oil; 0.032 mol) in dimethyl sulfoxide (25 ml) and benzene (40 ml) was heated at 90°C, under an argon atmosphere, for forty five minutes, to produce the methylsulfinyl carbanion. After allowing the mixture to come to room temperature, (methoxymethyl)triphenylphosphonium chloride (11.83 g, 0.035 mol) was

added and the mixture stirred for twenty minutes. To the deep red methoxymethylenetriphenylphosphorane solution, the aldehyde 38 (1.75 g, 0.012 mol) was added. After stirring for fifteen hours, the mixture was poured into ice water (100 ml) and extracted with ether (4 x 100 ml). The organic solution was washed with saturated sodium chloride solution, dried (magnesium sulfate), filtered and concentrated. The residue was vacuum distilled (80°C/3.5 torr) to remove triphenylphosphine oxide. The distillate was purified by flash chromatography on silica gel, using 0.5% ether in petroleum ether. The product 49 (2.89 g, 70% yield) was a mixture of the cis and trans isomers which gave the following spectral data: ir 1656 (olefin) and 1208 cm^{-1} (vinyl ether); nmr δ 6.30, 5.88 (both m, 1H, $-CH=C\underline{H}OCH_3$), 5.22 (br. s, 1H, -HC=), 4.72, 4.36 (both m, 1H, $-C\underline{H}=CHOCH_3$), 3.58, 3.50 (both s, 3H, $-CH=CHOC\underline{H}_3$), 1.60 (m, 3H, $CH_3\overset{1}{C}=$), 1.00 (s, 3H, $-CH_3$), and 0.80 (m, 3H, $-CH_3$); ms M^+ 180.1509 (calcd. for $C_{12}H_{20}O$: 180.1514).

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.93; H, 11.19; Found: C, 80.05; H, 11.31.

2-Hydroxy-6,6-dimethyl-7-methylenebicyclo[3.2.1]-octane (51)

At 0°C, aqueous 30% perchloric acid (40 ml) was added to a solution of the vinyl ether 49 (1.20 g, 6.67 mmol) in ether (50 ml), in a separatory funnel. After shaking for ten minutes, the acid was neutralized with saturated aqueous sodium bicarbonate solution. The product was extracted with dichloromethane (4 x 40 ml). The organic solution was washed with saturated sodium chloride solution, dried (magnesium sulfate), filtered and concentrated to give the alcohol 51 (1.01 g, 91% yield): ir 3390 (alcohol) and 1650 cm^{-1} (double bond); nmr δ 4.88 (s, 2H, $=CH_2$), 3.66 (m, 1H, -CHOH), 2.70 (br. s, 1H, -CHOH), 1.14 (s, 3H, $-CH_3$), and 1.06 (s, 3H, $-CH_3$); ms M^+ 166.1356 (calcd. for $C_{11}H_{18}O$: 166.1358).

Treatment of the vinyl ether 49 with hydrochloric acid, trifluoroacetic acid and oxalic acid also afforded alcohol 51 as the main product, in yields ranging from 50 to 80%.

Ethyl 2,3-epoxy-4-(2,2,3-trimethyl-3-cyclopentenyl)-butyrate (53)

At -78°C, a solution of n-butyl lithium in toluene (2 M, 3.98 ml, 7.96 mmol), diluted with tetrahydrofuran

(2 ml), was added dropwise to a solution of bis(trimethylsilyl)amine (1.86 ml, 8.66 mmol) in tetrahydrofuran (3 ml) under an argon atmosphere. After thirty minutes, ethyl bromoacetate (0.82 ml, 7.17 mmol) in tetrahydrofuran (2 ml) was added. After an additional twenty minutes, the aldehyde 38 (950 mg, 6.25 mmol) in tetrahydrofuran (3 ml) was added. After the mixture was stirred at -78°C for one hour, it was allowed to come to room temperature and stirred for four hours. The mixture was poured onto ice water and extracted with ether (4 x 20 ml). The organic solution was washed with 0.5 N hydrochloric acid and water, dried (magnesium sulfate and potassium carbonate), filtered and concentrated. Flash chromatography on silica gel, using 3% ether in petroleum ether, afforded the glycidic ester 53 (518 mg, 54% based on consumed starting material); ir 1680 (olefin) and 1760 cm^{-1} (ester); nmr δ 5.25 (br. s, 1H, -HC=), 4.25 (q, 2H, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 3.52 (m, 1H, $-\overset{|}{C}\underline{H}COO-$), 3.20 (m, 1H, $-\overset{|}{C}\underline{H}O-$), 1.60 (br. s, 3H, $CH_3\overset{|}{C}=$), 1.30 (t, 3H, J = 7 Hz, $-COOCH_2C\underline{H}_3$), 1.00 (s, 3H, $-CH_3$), and 0.75 (s, 3H, $-CH_3$); ms M^+ 238.1560 (calcd. for $C_{14}H_{22}O_3$: 238.1569).

2,3-Epoxy-4-(2,2,3-trimethyl-3-cyclopentenyl)butyric acid (54)

Aqueous 1 M sodium hydroxide (5 ml) was added to a solution of the glycidic ester 53 (600 mg, 2.52 mmol) in 98% ethanol (8 ml). After stirring for thirty minutes at room temperature, saturated sodium chloride solution (20 ml) was added and the solution extracted with ether (4 x 10 ml). The organic solution was dried (magnesium sulfate), filtered and concentrated to give the sodium salt of the acid. The salt was dissolved in ether and the solution acidified with 1 N hydrochloric acid, washed with water, dried (magnesium sulfate), filtered and concentrated. The resulting glycidic acid 54 (410 mg, 78% yield) gave the following spectral data: nmr δ 9.35 (br. s, 1H, -COOH), 5.20 (br. s, 1H, -HC=), 3.50 (m, 1H, -$\underline{\text{C}}$HCOO-), 3.20 (m, 1H, -$\underline{\text{C}}$HO-), 1.55 (br. s, 3H, $CH_3\overset{|}{C}=$), 0.92 (s, 3H, $-CH_3$), and 0.62 (s, 3H, $-CH_3$).

3-(2,2,3-Trimethyl-3-cyclopentenyl)propionaldehyde (50) and 3-(2,2,3-Trimethyl-3-cyclopentenyl)propionic acid (57)

At 0°C, aqueous 30% perchloric acid (10 ml) was added to the vinyl ether 49 (400 mg, 2.22 mmol) in ether (25 ml). After stirring vigorously for four minutes, ice cold 0.5 N sodium hydroxide solution

(10 ml) was added. The mixture was extracted with dichloromethane (4 x 15 ml). The organic solution was washed with saturated sodium chloride solution, dried (sodium sulfate), filtered and concentrated. A small sample of pure aldehyde 50 was obtained by column chromatography on silica gel, using 5% ether in petroleum ether, and gave the following spectra data: [ir 2720 and 1710 cm^{-1} (aldehyde); nmr δ 9.80 (t, 1H, J = 2 Hz, -CHO), 5.24 (br. s, 1H, -HC=), 1.62 (m, 3H, $CH_3\overset{|}{C}=$), 1.00 (s, 3H, $-CH_3$), and 0.80 (s, 3H, $-CH_3$)]. The aldehyde 50 was found to be rather unstable, resulting in substantial loss of material during the purification. For the subsequent experiment, the crude product was used directly without purification. Crude aldehyde 50 was dissolved in 98% ethanol (10 ml). This mixture was added dropwise to a solution of Tollen's reagent (50 ml), prepared by adding aqueous 6 N ammonium hydroxide (10 ml) to a mixture of aqueous solutions of silver nitrate (10%, 20 ml) and sodium hydroxide (10%, 20 ml). After stirring at room temperature for one hour, the neutral compounds were extracted with dichloromethane (4 x 10 ml). The ice cold aqueous layer was acidified with concentrated hydrochloric acid and then extracted with dichloromethane (4 x 10 ml). This organic solution was washed

with saturated sodium chloride solution, dried (sodium sulfate), filtered and concentrated to afford the acid 57 (158 mg, 39% yield from 49): ir 3300-2700 and 1710 cm^{-1} (acid); nmr δ 11.14 (br. s, 1H, -COOH), 5.22 (br. s, 1H, -HC=), 1.60 (m, 3H, $CH_3\overset{|}{C}=$), 1.00 (s, 3H, $-CH_3$), and 0.78 (s, 3H, $-CH_3$); ms M^+ 182.1308 (calcd. for $C_{11}H_{18}O_2$: 182.1307).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.48; H, 9.96; Found: C, 72.70; H, 10.07.

Methyl 3-(2,2,3-trimethyl-3-cyclopentenyl)propionate (58)

A mixture of the acid 57 (62 mg, 0.34 mmol) and anhydrous potassium carbonate (171 mg, 1.24 mmol) in acetone (20 ml) was stirred at room temperature, under an argon atmosphere, for forty minutes. Methyl iodide (0.11 ml, 1.78 mmol) was added and the reaction mixture refluxed overnight. The mixture was diluted with water and extracted with dichloromethane (4 x 15 ml). The organic solution was washed with saturated sodium chloride solution, dried (sodium sulfate), filtered and concentrated. The residue was purified by flash chromatography on silica gel, using 2% ether in petroleum ether. The resulting ester 58 (40 mg, 60% yield) gave the following spectral data: ir 1742 (ester) and 1620 cm^{-1} (olefin); nmr δ 5.22 (br. s, 1H, -CH=), 3.68 (s,

3H, $-COOCH_3$), 1.60 (m, 3H, $CH_3\overset{|}{C}=$), 1.00 (s, 3H, $-CH_3$), and 0.80 (s, 3H, $-CH_3$); ms M^+ 196.1462 (calcd. for $C_{12}H_{20}O_2$: 196.1463).

1-Methoxy-3-(2,2,3-trimethyl-3-cyclopentenyl)propane (59)

Potassium acetate (150 mg, 1.53 mmol) and 5% palladium on carbon (55 mg) were added to a solution of the vinyl ether 49 (554 mg, 3.08 mmol) in ethyl acetate (100 ml). The mixture was stirred at room temperature, under an atmosphere of hydrogen, for one hour. After filtering off the catalyst, the solvent was removed to give the ether 59 (545 mg, 97% yield): ir 1645 (olefin) and 1122 cm^{-1} (ether); nmr δ 5.24 (br. s, 1H, -HC=), 3.40 (m, 5H, $-CH_2OCH_3$), 1.62 (m, 3H, $CH_3\overset{|}{C}=$), 0.98 (s, 3H, $-CH_3$), and 0.76 (s, 3H, $-CH_3$); ms M^+ 182.1668 (calcd. for $C_{12}H_{22}O$: 182.1671).

5-(3-Methoxypropyl)-6,6-dimethyl-2-cyclohexenone (61)

At -78°C, ozone (condition: E = 80V, air inlet = 8 psi, ozone outlet = 0.06 psi) was allowed to pass through a solution of the ether 59 (1.19 g, 6.54 mmol) in methanol (10 ml) and dichloromethane (10 ml) until a light blue color was retained (about twenty minutes). Glacial acetic acid (15 ml) and zinc dust (2.12 g, 32.62 mmol) were added to the solution under an argon

atmosphere. The mixture was allowed to come to room temperature and stirred for three hours. After filtering off the zinc, the organic solution was washed with ice cold 0.05 N sodium hydroxide solution (2 x 50 ml), saturated sodium sulfite solution (50 ml), and water (50 ml), dried (magnesium sulfate), filtered and concentrated. The crude keto aldehyde 60 (1.24 g), without purification, was dissolved in benzene (25 ml). p-Toluenesulfonic acid (80 mg, 0.46 mmol) was added and the mixture refluxed under an argon atmosphere for three hours with continuous removal of water using a Dean-Stark water separator. After removal of the solvent, the residue was purified by flash chromatography on silica gel. Elution with 20% ether in petroleum ether gave the keto ether 61 (0.72 g, 56% yield); ir 1675 (α,β-unsaturated ketone) and 1118 cm^{-1} (ether); nmr δ 6.84 (ddd, 1H, J = 10, J' = 5, and J" = 3 Hz, -COCH=CH-), 5.94 (td, 1H, J = 10 and J' = 2 Hz, -COCH=CH-), 3.38 (m, 5H, $-CH_2OCH_3$), 1.18 (s, 3H, $-CH_3$) and 1.00 (s, 3H, $-CH_3$); ms M^+ 196.1462 (calcd. for $C_{12}H_{20}O_2$: 196.1463).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.41; H, 10.28; Found: C, 73.40; H, 10.32.

5-(3-Bromopropyl)-6,6-dimethyl-2-cyclohexenone (64)

Boron tribromide (0.41 ml, 4.29 mmol) was slowly added to a solution of the keto ether 61 (280 mg, 1.43 mmol) in dichloromethane (25 ml). The mixture was stirred overnight under an argon atmosphere. After water (5 ml) was added, the mixture was extracted with ether (4 x 15 ml). This organic solution was washed with saturated sodium chloride solution and water, dried (magnesium sulfate), filtered and concentrated. Flash chromatography of the residue on silica gel, using 15% ether in petroleum ether, afforded the bromide 64 (272 mg, 78% yield): 1675 cm^{-1} (α,β-unsaturated ketone); nmr δ 6.80 (ddd, 1H, J = 10, J' = 5, and J" = 3 Hz, -COCH=CH-), 5.94 (td, 1H, J = 10 and J' = 2 Hz, -COCH=CH-), 3.44 (t, 2H, J = 6 Hz, $-CH_2Br$), 1.18 (s, 3H, $-CH_3$), and 1.00 (s, 3H, $-CH_3$); ms M^+ 244.0464 and 246.0445 (calcd. for $C_{11}H_{17}OBr$: 244.0462 and 246.0442).

5-(3-Hydroxypropyl)-6,6-dimethyl-2-cyclohexenone (62)

Silver carbonate (683 mg, 2.47 mmol) and water (8 ml) were added to a solution of the bromide 64 (200 mg, 0.82 mmol) in tetrahydrofuran (10 ml). The mixture was heated for fifty hours at 50°C. The resulting mixture was filtered through a Celite pad, dried (sodium

sulfate), filtered and concentrated. The crude product was purified by flash chromatography on silica gel. Elution with 70% ether in petroleum ether gave pure 62 (79 mg, 53% yield): ir 3430 (alcohol) and 1673 cm^{-1} (α,β-unsaturated ketone); nmr δ 6.86 (ddd, 1H, J = 10, J' = 5, and J" = 3 Hz, -COCH=CH-), 5.96 (td, 1H, J = 10 and J' = 2 Hz, -COCH=CH-), 3.68 (t, 2H, J = 6 Hz, $-CH_2OH$), 1.18 (s, 3H, $-CH_3$), and 1.00 (s, 3H, $-CH_3$); ms M^+ 182.1307 (calcd. for $C_{11}H_{18}O_2$: 182.1307).

6,6-Dimethyl-5-(3-oxopropyl)-2-cyclohexenone (47)

To a suspension of pyridinium chlorochromate (418 mg, 1.94 mmol) in dichloromethane (3 ml) under an argon atmosphere, was added the keto alcohol 62 (70 mg, 0.38 mmol) in dichloromethane (3 ml). The mixture was stirred at room temperature for ninety minutes. Ether (3 ml) was added and the mixture filtered through a short pad of florisil. Removal of the solvent afforded the pure keto aldehyde 47 (65 mg, 96% yield), which gave the following spectral data: ir 2720, 1723 (aldehyde) and 1673 cm^{-1} (α,β-unsaturated ketone); nmr δ 9.78 (t, 1H, J = 1 Hz, -CHO), 6.82 (ddd, 1H, J = 10, J' = 5, and J" = 3 Hz, -COCH=CH-), 5.94 (td, 1H, J = 10 and J' = 2 Hz, -COCH=CH-), 1.18 (s, 3H, $-CH_3$), and 1.00

(s, 3H, $-CH_3$); ms M^+ 180.1150 (calcd. for $C_{11}H_{16}O_2$: 180.1150).

5-(2-Carboxyethyl)-6,6-dimethyl-2-cyclohexenone (67)

The keto alcohol 62 (50 mg, 0.27 mmol) was dissolved in acetone (5 ml) and chilled to 0°C. A solution of 8 N Jones reagent (about 2 ml) was added dropwise until an orange color was retained. After stirring for thirty minutes, the reaction mixture was extracted with dichloromethane (4 x 10 ml). The organic solution was washed with saturated sodium chloride solution, dried (magnesium sulfate), filtered and concentrated to give the keto acid 67 (52 mg, 96% yield): 3200-2800, 1709 (acid) and 1673 cm^{-1} (α,β-unsaturated ketone); nmr δ 8.90 (br. s, 1H, -COOH), 6.84 (ddd, 1H, J = 10, J' = 5, and J" = 3 Hz, -COCH=CH-), 5.96 (td, 1H, J = 10 and J' = 2 Hz, -COCH=CH-), 1.18 (s, 3H, $-CH_3$), and 1.00 (s, 3H, $-CH_3$); ms M^+ 196.1100 (calcd. for $C_{11}H_{16}O_3$: 196.1099).

5-(2-Carbomethoxyethyl)-6,6-dimethyl-2-cyclohexenone (68)

A mixture of the keto acid 67 (57 mg, 0.29 mmol) and anhydrous potassium carbonate (140 mg, 1.01 mmol) in acetone (5 ml) was stirred vigorously at room temperature, under an argon atmosphere, for one hour.

Methyl iodide (0.10 ml, 1.62 mmol) was added and the mixture refluxed overnight. After the excess methyl iodide was removed by distillation, water was added and the product extracted with dichloromethane (4 x 5 ml). The organic layers were washed with saturated sodium chloride solution, dried (sodium sulfate), filtered and concentrated. Flash chromatography of the residue on silica gel, using 20% ether in petroleum ether, afforded the keto ester 68 (42 mg, 69% yield): ir 1738 (ester) and 1675 cm^{-1} (α,β-unsaturated ketone); nmr δ 6.82 (ddd, 1H, J = 10, J' = 5, and J" = 3 Hz, -COCH=C<u>H</u>-), 5.94 (td, 1H, J = 10 and J' = 2 Hz, -CO<u>C</u>H=CH-), 3.68 (s, 3H, $-COOCH_3$), 1.18 (s, 3H, $-CH_3$) and 1.00 (s, 3H, $-CH_3$); ms M^+ 210.1257 (calcd. for $C_{12}H_{18}O_3$: 210.1256).

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